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SYNTHESIS AND CHARACTERISATION OF OCTAHYDROACRIDINE BASED IMIDAZOLIUM SALT

Aminu Ahmed
Department of Chemistry, Kano University of Science and Technology Wudil
Correspondence author: aahmedte64@yahoo.com,

ABSTRACT
This paper describes the synthesis and characterization of chiral octahydroacridine based imidazolium salt. The reaction of cyclohexanone, dimethylamine hydrochloride and formaldehyde under reflux affords 2-Dimethylaminomethylcyclohexanone which undergoes reaction with cyclohexanone to give 2, 2′-Dicyclohexanoylmethane. Reaction of 2, 2′-dicyclohexanoylmethane with hydroxylamine hydrochloride affords the synthesis of Sym-Octahydroacridine from which 4-chlorooctahydroacridine was obtained by oxidation, hydrolysis and halogenation of the resulting secondary alcohol. The desired chiral octahydroacridine based imidazolium salt was prepared by refluxing of mesityl imidazole and 4-chlorooctahydroacridine in THF at 90 °C in a pressure tube for two week allowing the synthesis of a new unreported chiral bidentate NHC ligand precursor.

Keywords: Nucleophilic heterocyclic carbene (NHC), octahydroacridine, ligand, mesityl imidazole

INTRODUCTION

The chemical versatility of N-heterocyclic carbenes (NHC) has yielded a large number of new compounds with improved catalytic applications. Despite the design of NHC-based homogenous catalysts being relatively recent, the interest in the area has increased dramatically that we can now find many reviews regarding their preparations and catalytic properties (Mas-Marza *et al*, 2005). Along this line ligand designs have been largely depended on the type of catalysis to be carried out resulting in the use of chiral carbenes in asymmetric catalysis in1996/1997 by Herrmann *et al* 2000, chemists have pursued this area leading to many publications on the use of NHCs for asymmetric homogeneous catalysis [Crabtree, 2006]. Herrmann applied the NHC and their derivatives in catalysed asymmetric nucleophilic acylation, processes with remarkable success.

Chiral NHC ligands have found applications in the following catalytic processes: Pd(II) NHC in Heck reaction [Yagyu *et al,* 2006], olefin metathesis [Fournier and Collins, 2007], Rh (I) and Ir (I)-transfer hydrogenation of ketones [Crabtree, 2006].

In addition to the pyridine functionalised imidazolium salts so far reported [Danopoulos *et al*, 2002], it was of interest to form a ligand that would have increased hemilability as well as a chiral aspect for catalytic applications. The aromaticity and lack of sp^3 hybridized carbons of quinoline and pyridine based systems made them unsuitable for the task, thus octahydroacridine was thought to be a suitable candidate. Octahydroacridine can offer a secondary donor function for chelation as well as sp^3 hybridized carbons. These tetrahedral carbons can offer the ability to make the ligand chiral as well as provide a framework for the addition of extra steric bulk if needed. It is expected that the desired imidazolium salt will give access to useful transition metal carbene complexes that may be used in many catalytic applications.

MATERIALS AND METHODS

This research work was carried out at Cardiff University, Wales, United Kingdom.

Unless otherwise stated all manipulations were carried out using standard Schlenk techniques under an atmosphere of dry argon or in nitrogen glove box. Glassware were dried overnight in an oven at 120^{o}C or flame dried prior to use. Tetrahydrofuran (THF), diethyl ether (Et_2O), and n-hexane were dried and degassed by refluxing under dinitrogen and over sodium wire and benzophenone. Dichloromethane (DCM), methanol (MeOH) and acetonitrile (MeCN) were dried over calcium hydride. All other anhydrous solvents were obtained by distillation from the appropriate drying agent under dinitrogen. Deoxygenation of solvents and reagents was carried by freeze thaw degassing.

All NMR solvents were purchased from Aldrich and Goss, dried over 3A molecular sieve and freeze-thaw degassed three times. All reagents were purchased from commercial sources and used without purification, unless otherwise stated.

All NMR data are quoted δ/ppm. ^{1}H and ^{13}C spectra were recorded on a Bruker 400 MHz DPX Avance, unless otherwise stated, and referenced to $SiMe_4$. Electrospray mass spectrometry (ESMS) was performed on a VG Fisons Platform II instrument by the department of Chemistry, Cardiff University. Micro analysis was performed by Warwick Analytical Service.

Synthesis of 2-Dimethylaminomethylcyclohexanone (1):

A mixture of cyclohexanone (22.3g, 0.23 mol), dimethylamine hydrochloride (9.9 g, 0.12 mol), and formaldehyde (36.9 g of 37% solution in water) was refluxed (oil bath at 130 oC, 30 min) and then cooled to room temperature. Sodium chloride (4.25g) was added, and the mixture was stirred at 23 0C (20 min).

The mixture was transferred to separatory funnel, and the organic phase and aqueous phase were separated. The aqueous phase was extracted with Et_2O (4 X 10 mL) to further remove unreacted cyclohexanone. The aqueous phase was adjusted to pH13.5 by addition of 9.5 g of KOH in 22.5 mL of water. The mannich base was separated as yellow oil from the upper layer, which exhibited a strong amine odour. The aqueous phase was extracted with Et_2O (3 x 20 mL), and yellow oil and the ether extracts were combined and then dried with anhydrous sodium sulphate. After removal of the ether at 23 ^oC under reduced pressure, the remaining oil was distilled under vacuum (42-43 ^oC/100 mTorr): yield 16.0 g (90%).^{1}H NMR ($CDCL_3$-d3:400 MHz R.T): d=1.3-2.7(m, 17H), ^{13}C NMR (DCM, 400MHz R.T.): 24.30, 27, 80, 32.23, 41.69, 45.57, 48.73, 58.80, 212.27.

Synthesis of 2, 2'-Dicyclohexanoylmethane (2):
2-Dimethylaminomethylcyclohexanone (19.5 g, 0.125 mol) and cyclohexanone (37 g, 0.38 mol) were mixed and refluxed (oil bath at 205 ^oC, 1.5 h), and the resulting mixture was distilled under vacuum. The fraction collected at 90-100 ^oC/ 100 mToor was colourless oil (20.75g).Hexane (25mL) was added to the oil and mixture was cooled to -30 ^oC overnight. A white solid was collected and washed with cold hexane (3 x 15 mL). The colourless solid product was obtained: yield 14.63 (56.2%).^{1}H NMR ($CDCL_3$:400 MHz R.T): d = 1.0-2.4(m, 17H): ^{13}C NMR (DCM, 400MHz R.T.): 24.37, 24.60, 27.56, 29.11, 29.88, 33.88, 34.68, 41.44, 41.77, 47.18, 48.33, 212.33, 212.83.

Synthesis of Sym-Octahydroacridine (3):
Hydroxylamine hydrochloride (7.63 g, 0.11 mol) was added with stirring to a boiling solution of 2, 2'-Dicyclomethane (14.125g, 0.068mol) in EtOH (100 Ml). The mixture was refluxed (20 min), then the ethanol was removed under reduced pressure, and 25 mL of water was added to dissolve the residue. A solution of NaOH (5g in 25 mL of water) was added at 0 ^oC to bring the pH of the solution to 13.5. The solid that appeared was collected and washed with water and dried. Yield 11.7 g (92 2%).^{1}H NMR ($CDCL_3$-d3:400 MHz R.T): d = 1.71-2.84(m, 16H), 7.00 (s 1H): ^{13}C NMR (DCM, 400MHz R.T.): 22.53, 22.95, 27.98, 31.75, 128.85, 137.14, 153.51.

Synthesis of Sym-Octahydroacridine N-Oxide (4):
A mixture of sym-Octahydroacridine (11.5 g, 0.062 mol) and 3-chloroperoxybenzoic acid (17.75 g, 77% max) in $CHCl_3$ (100ml) was stirred (17h) at 23 ^oC. The resulting reaction mixture was extracted with $NaHCO_3$ (32.5 g) and Na_2CO_3 (15 g) in water (350 mL). The aqueous phase (pH = 8.5) was washed with CH_2Cl_2 (2 x 75 mL), and the chloroform and dichloromethane solutions were combined and dried with anhydrous sodium sulphate. After removal of the solvent at 23 ^oC under reduced pressure, the product sym-octahydroacridine N-oxide was obtained as a light yellow solid: yield 12.0 g (96.3%).^{1}H NMR ($CDCL_3$-d3:400 MHz R.T): d = 1.55-1.74 (m, 8H), 2,52-2.80(m, 8H), 6.7(s, 1H): ^{13}C NMR ($CDCl_3$, 400MHz R.T.): 21.19, 21.44, 24.11, 27.58, 125.58, 131.10.

Synthesis of 1, 2, 3, 4, 5, 6, 7, 8-octahydroacridin-4-ol (5):
Triflouroacetic anhydride (10.2Ml, 0.072mol, 2.5 equivalent) was slowly added to a stirred solution of octahydroacridine N-oxide (5.85g, 0.0288mol) in dry dichloromethane (DCM) (50mL) causing a slight increase in temperature of the solution. The solution was allowed to stir for a further hour at room temperature. The volatiles were then removed under reduced pressure to leave a yellow viscous residue, which was taken up in 20ml DCM. This was then saponified by the addition of a 2M solution of sodium carbonate, the biphasic mixture being vigorously stirred for 3 hours. The organic phase was then separated and the aqueous phase washed twice with DCM. The combined organic extract extracts were then washed with water and brine and then dried over magnesium sulphate. The solvent was removed to give octahydroacridine-4-ol (4.98g, 85%). ^{1}H NMR ($CDCl_3$, 400MMH_Z, δ): 7.05(s, IH, ArH), 4.55(m, 1H, CHOH), 4.05(Br s, 1H, CHOH), 2.8(m, 2H, CH_2), 2.7(m, 4H, CH_2), 2.2(m, 1H, CH_2), 1.6-2.0(m,7H, CH_2). ^{13}CNMR ($CDCl_3$, 100MH_Z, δ): 154.86, 154.35, 137.5, 130.97, 128.55, 68.36, 31.88, 31.15, 28.42, 27.99, 23.16, 22.79, 19.39.

Synthesis of 4-chlorooctahydroacridine (6):
Thionyl chloride (15mL) in $CHCl_3$ (15mL) was added to a solution of octahydroacrin-4-ol (7g, 0.0345mol) in 25mL DCM. The mixture was stirred at room temperature for 10 minutes, and then refluxed for an hour at 80 ^oC. The excess thionyl chloride and volatile by-products were then removed under reduced pressure and the residue dissolved in DCM (75mL). The solution was then extracted with Na_2CO_3 (7.5g) in water (125mL) and the aqueous phase (pH 8.5) was washed with DCM (2x100mL). The DCM extract was then dried with Na_2CO_3 and the solvent removed under reduced pressure to give a yellow solid of 4-chlorooctahydroacridine (4.90g, 64%). ^{1}H NMR ($CDCl_3$, 400MMH_Z, δ): 7.05 (s, 1H, ArH), 5.20 (m, 1H, CHCl), 2.55-2.95(m, 6H, CH2), 2.05-2.35(m, 3H, CH2), 1.65-1.85 (m, 5H, CH2). ^{13}CNMR ($CDCl_3$, 100MH_Z, δ): 155.53, 151.22, 137.96, 132.35, 128.97, 59.44, 32.65, 32.24, 28.60, 27.54, 23.15, 22.65, 17.42.

Synthesis of 1-mesityl-3-octahydroacridinimidazolium chloride (7):
4-chlorooctahydroacridine (1g, 4.5mmol) and mesityl imidazole (0.84g, 4.5mmol) were placed in an ACE pressure tube with 10 mL THF.The mixture was refluxed at 90 ^oC for 10 days as a dark precipitate formed. The precipitate was filtered and washed with Et_2O (4x10mL) to give off white solid of the imidazolium salt (0.15g, 8%).

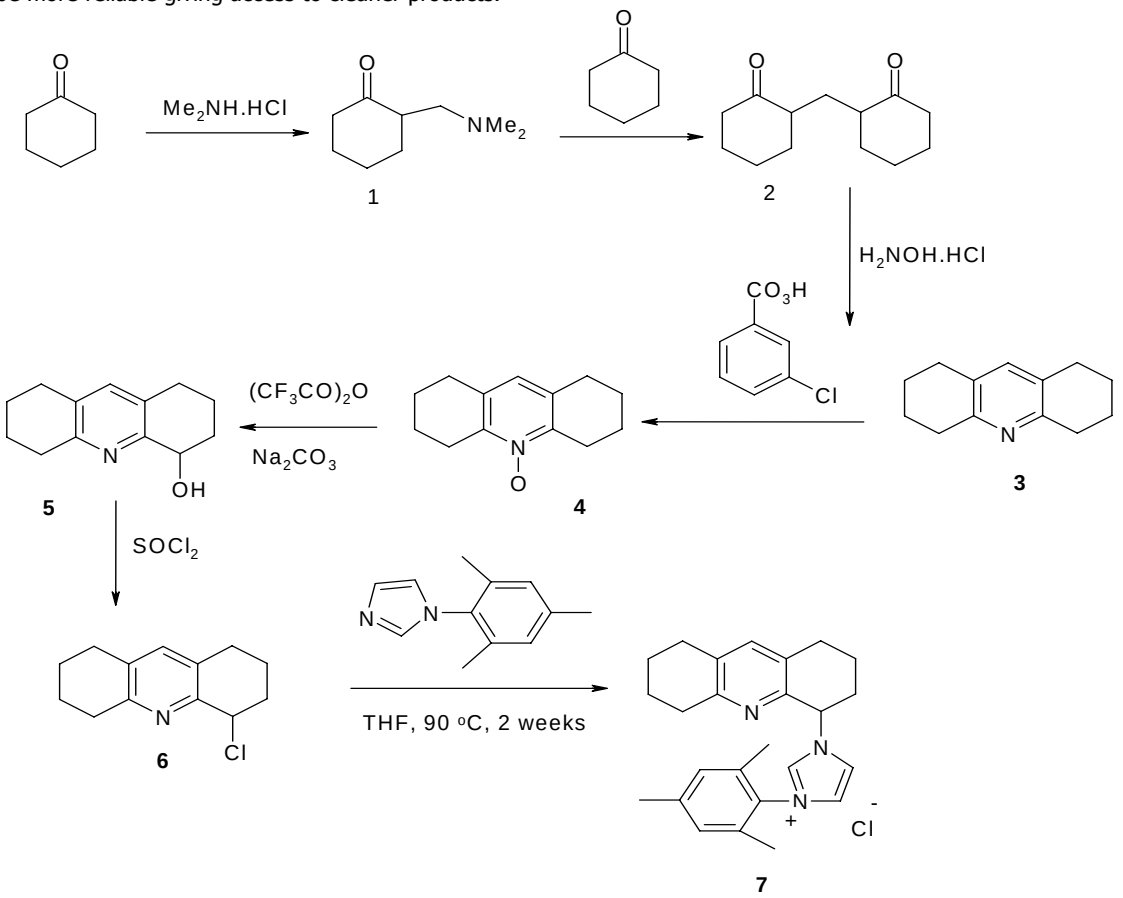
The filtrate was placed back under reflux where it continued to react further over time required for $C_{25}H_{29}N_3Cl$: C, 73.80; H, 7.13; N, 10.33%. Found: C, 73.65; H, 7.11; N, 9.98%. ^{1}H NMR ($CDCl_3$, 400MMH_Z, δ): 10.15 (s, 1H, NCHN), 8.18(s, 1H, CHHC), 7.65(s, 1H, CHHC), 7.20(s, 1H, ArH), 6.95 (m, 2H, ArH), 6.55 (s, 1H, CHN), 1.80-3.40 (m, 23H, CH_2, CH_3). **MS**(ES) m/z (%): 372.3(29) $[M\text{-}Cl]^+$; **MS** (ESI) m/z (%): found 372.3424 $[M\text{-}Cl]^+$; expected: 372.5333.

DISCUSSION

Octahydroacridine was synthesized following the procedures of Paine et al 2000 and Pilato et al 2001. Pilato's method offers fewer synthetic steps as well less forcing conditions but the yield as stated in the paper (50%) could only be achieved by strict adherence to condition and deviation from the procedure led to the formation of large by products.

Though Paine's method requires the use of many steps and forcing reaction conditions, it was found to be more reliable giving access to cleaner products.

The Paine's synthetic procedure as well as steps leading to the synthesis of the desired imidazolium salt is depicted in Scheme 2.8 above. To introduce the chlorine onto position 4 it was necessary to functionalise the octahydroacridine ring with hydroxyl group. Paine's procedure involves the reaction of octahydroacridine with 3-chloroperoxybenzoic to form octahydroacridine N-oxide which upon reaction with an excess of boiling acetic anhydride gave 4-hydroxyl substituted octahydroacridine **5** after work up. However, in our work triflouroacetic anhydride was used instead of large excess of acetic anhydride with the reaction being carried out at room temperature to form the desired 4-hydroxyoctahydroacridine (Fontena *et al* 1995). 4-Chlorooctahydroacridine **6** was prepared by the reaction of 4-hydroxyoctahydroacridine with thionyl chloride in DCM which upon work up gave the desired compound **7** as a yellow solid.



Scheme 1: **Synthesis of octahydroacridine based imidazolium salt**

Finally the acridine based salt was prepared by reaction of 4-chlorooctahydroacridine with 1-mesitylimidazol in THF in a pressure tube at 90 ^oC for 14 days. The yield obtained in this reaction was very low because the reaction follows a typical SN_2 pathway, and with secondary alkyl chloride, the reaction would be expected to be very slow even under the forcing conditions used. Attempt to prepare a more reactive 4 iodooctahydroacridine was made by the addition of sodium iodide to an acetone solution of 4-chlorooctahydroacridine and stirred overnight and after work up there was no observable effect from the ^{1}H NMR spectra.

The imidazolium salt prepared was fully characterised by ^{1}H NMR, mass spectroscopy and micro analysis with the ^{1}H NMR showing C2-H appearing as singlet at a δ value of 10.15pmm. The imidazolium salt **7** returned satisfactory MS and elemental analysis results.

Due to low yield and time constrain large varieties of the acridine based imidazolium could not be prepared using the secondary alkyl chloride **6**. However, it should be noted that, there is a lot of research opportunities in this area that need to be explored. It is envisaged that once a more reactive halooctahydroaricdine such as bromo or iodooctahydroacridine can be prepared, 1-acridine imidazole can be obtained by coupling with alkyl halides thereby opening the way to access a range of acridine based imidazolium ligands.

Conclusion

A reproducible method has been developed for the preparation of 1, 2, 3, 4, 5, 6, 7, 8-octahydroacridine and its subsequent conversion to 4-chloroochydrooctahydroacridine. The less reactive alkyl halide was reacted with mesityl imidazole to prepare the chiral octahydrooctahydroacridine based imidazolium salt giving access to new bidentate carbene precursor and its metal complexes may be efficient in asymmetric homogenous catalysis, Suzuki coupling and Heck coupling reactions.

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